REMARKS

The specification of the application has been amended to recite the serial numbers of the applications entitled "Methods of Administering/Dosing Anti-RSV Antibodies For Prophylaxis and Treatment," filed on November 28, 2001. The amendments to the specification do not constitute new matter.

Claims 1-86 were pending in this application. Applicants note with appreciation that the elected substitution of tyrosine at position 252 is free of the prior art. Applicants also note that the restriction requirement was made final and thus, claims 1, 5, 6, 9, 13, 17, 21-57, 59-68 and 70-85, drawn to a non-elected invention, were withdrawn from consideration. In view of their withdrawal from consideration, claims 1, 5, 6, 9, 13, 17, 21-57, 59-68 and 70-85 have been canceled, without prejudice to Applicants' right to pursue the subject matter of the canceled claims in related applications. Applicants have also canceled claims 2-4, 7, 8, 10-12, 14-16, 18-20, 58, 69 and 86, without prejudice to Applicants' right to pursue the subject matter of the canceled claims in related applications, and added new claims 87-116, directed to the elected subject matter. Upon entry of this Amendment, claims 87-116 will be pending. The new claims are fully supported by the specification of the present application (see, *e.g.*, page 4, line 21 to page 8, line 16, page 14, line 1 to page 20, line 19, page 24, lines 10-14, page 25, line 31 to page 26, line 9, Table II, and Table III of the specification), and do not constitute new matter.

Entry of the foregoing amendments and consideration of these remarks are respectfully requested.

1. CONSIDERATION OF REFERENCES

Applicants note that the Examiner did not consider references AA-CZ cited on the revised PTO 1449 Form filed on September 26, 2002 in the United States Patent and Trademark Office because the Examiner was unable to find the revised PTO 1449 Form and the copies of references AA-CZ. In accordance with the Examiner's advice on page 3 of the Office Action mailed April 7, 2004, Applicants submit herewith a copy of the Information Disclosures Statement, a copy of the revised PTO 1449 Form and copies of references AA-CZ filed on September 26, 2002. Applicants respectfully request that the Examiner consider references AA-CZ.

2. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 2-4, 7-8, 10-12, 14-16, 18, 19, 20, 58 69 and 86 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. For the reasons detailed below, the rejections under 35 U.S.C. § 112, second paragraph, cannot stand and should be withdrawn.

The Examiner contends that the recitation "modification of IgG at position 251-256" without reference to providing a sequence identifier renders claims 2 and 3 indefinite. In particular, the Examiner contends that the recitation of amino acid positions from the first amino acid of a protein without providing sequence identifiers for the protein is indefinite and ambiguous because different laboratories may have different numbering of the same protein. Applicants have canceled claims 2 and 3, without prejudice, and added new independent claims 87-91 (and claims dependent therefrom) that recite a modified IgG comprising an IgG constant domain comprising amino acid substitutions at specific amino acid residue positions. Applicants respectfully point out that the specification of the application at page 4, line 31 to page 5, line 1 states that "all residues of the IgG constant domain are numbered according to Kabat *et al.* (Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services, 1991 ...) and as presented in Figure 2 (SEQ ID NO:83), and include corresponding residues of other IgG constant domains as determined by sequence alignment." Accordingly, Applicants respectfully assert that one of skill in the art would appreciate that amino acid positions recited in the claims are amino acid residues of an IgG constant domain numbered according to Kabat and, therefore, would appreciate what amino acid residues are being modified in an IgG constant domain. In addition, it is well within the skill in the art to perform sequence alignments with known constant domains (such as presented in Figure 2 and Kabat) and determine the particular position of a residue according to the Kabat numbering system. Thus, Applicants respectfully assert that the rejection of claims 2 and 3 under 35 U.S.C. § 112, second paragraph, for the recitation of "modification of IgG at position 251-256" cannot stand and should be withdrawn.

The Examiner contends that the recitation of the trademark "SYNAGIS®" renders claim 19 indefinite. Applicants have canceled claim 19, without prejudice, and added new claim 105 (and claims dependent therefrom) that recites the term "palivizumab", not

"SYNAGIS®". Accordingly, Applicants respectfully assert that the rejection of claim 19 under 35 U.S.C. § 112, second paragraph, for the recitation of the trademark "SYNAGIS®" is moot.

The Examiner contends that the recitation of "A4B4L1FR-S28R" [sic] renders claim 20 indefinite. Applicants have canceled claim 20, without prejudice, and added new claim 106 (and claims dependent therefrom) that recites "the variable heavy domain and variable light domain of A4B4L1FR-S28R (SEQ ID NOS.: 48 and 11)." Applicants respectfully assert that reference to SEQ ID NOS.:48 and 11 in claim 106 is not necessary since Table III provides the sequence identifiers of the variable heavy domain and variable light domain of A4B4L1FR-S28R. However, in order to expedite the prosecution of this application and without conceding to the validity of the rejection, Applicants have recited the sequence identifiers of the variable heavy domain and variable light domain of A4B4L1FR-S28R in new claim 106. Accordingly, Applicants respectfully assert that the rejection of claim 20 under 35 U.S.C. § 112, second paragraph, for the recitation of the trademark "A4B4L1FR-S28R" is moot.

In view of the foregoing, Applicants assert that the rejections under 35 U.S.C. § 112, second paragraph, have been overcome and, therefore, respectfully request that the rejections be withdrawn.

3. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 19 and 20 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Examiner contends that Applicants must make SYNAGIS® and A4B4L1FR-S28R readily available to the public or obtainable by a repeatable method set forth in the specification. Applicants respectfully assert that SYNAGIS® is and was commercially available at the time the application was filed as evidenced by the enclosed product information from the 2001 and 2004 Physicians' Desk References (Exhibit A). Further, Applicants respectfully assert that the specification of the application sets forth a repeatable method for obtaining SYNAGIS® and A4B4L1FR-S28R, including disclosure of the amino acid sequences of these antibodies (see, *e.g.*, the specification at page 8, lines 2-16, page 34, line 30 to page 40, line 5, page 25, line 31 to page 26, line 9, Table II and Table III). Thus, SYNAGIS® and A4B4L1FR-S28R are enabled by

the specification. Accordingly, Applicants respectfully assert that the rejection under 35 U.S.C. § 112, first paragraph, cannot stand and should be withdrawn.

4. THE REJECTION UNDER 35 U.S.C. § 102(e) SHOULD BE WITHDRAWN

Claims 2-4, 7, 8, 10-12, 15, 16, 58 and 69 are rejected under 35 U.S.C. § 102(e) as being anticipated by Ward, U.S. Patent No. 6,277,375 ("Ward"). The Examiner contends that Ward teaches a modified human, humanized and non-human IgG comprising an IgG constant domain, wherein the modified IgG has an increased half-life compared to the half-life of an IgG having the wild-type IgG constant domain. Further, the Examiner contends that Ward teaches a modified IgG comprising an IgG constant domain with modifications at specific amino acid positions, including substitution of threonine at position 252, threonine at position 254 and threonine at position 256. For the reasons detailed below, the rejections under 35 U.S.C. § 102(e) cannot stand and should be withdrawn.

The legal test for anticipation under 35 U.S.C. § 102 requires that each and every element of the claimed invention be disclosed in a prior art reference in a manner sufficient to enable one skilled in the art to reduce the invention to practice, thus placing the public in possession of the invention. W.L. Gore Associates v. Garlock, Inc. , 721 F.2d 1540, 1554 (Fed. Cir. 1983); In re Donohue, 766 F.2d 531 (Fed. Cir. 1985).

In order to expedite prosecution of the application and without conceding to the validity of the rejection, Applicants have canceled claims 2-4, 7, 8, 10-12, 15, 16, 58 and 69, without prejudice, and have added new claims 87-116, directed to a modified IgG comprising an IgG constant domain comprising amino acid substitutions at specific amino acid residue positions. In particular, new independent claims 87-90 (and claims dependent therefrom) are directed to a modified IgG comprising a human IgG constant domain comprising amino acid substitutions at specific amino acid positions. New independent claim 91 (and claims dependent therefrom) is directed to a modified IgG comprising a non-human IgG constant domain comprising one or more substitutions at specific amino acid residues.

Independent claim 87 recites a modified IgG comprising a human IgG constant domain comprising one or more amino acid substitutions relative to a wild-type human IgG constant domain at one or more amino acid residues 251-256, 285-290, 308-314, 385-389 and 428-436, wherein the modified IgG has an increased half-life compared to the half-life of an IgG having the wild-type human IgG constant domain, and wherein an amino acid

substitution at amino acid residue 252 is a substitution with tyrosine, phenylalanine, tryptophan or threonine, an amino acid substitution at amino acid residue 254 is a substitution with threonine, an amino acid substitution at amino acid residue 256 is a substitution with serine, arginine, glutamine, glutamate, asparate, alanine, asparagine or threonine, an amino acid substitution at amino acid residue 309 is a substitution with proline, an amino acid substitution at amino acid residue 311 is a substitution with serine, an amino acid substitution at amino acid residue 433 is a substitution with lysine, arginine, serine, isoleucine, proline, glutamine or histidine, and an amino acid substitution at amino acid residue 434 is a substitution with histidine, asparagine, arginine, threonine, lysine or methionine.

Independent claim 88 recites a modified IgG comprising a human IgG constant domain comprising amino acid substitutions relative to a wild-type human IgG constant domain at amino acid residues 252, 254 and 256, wherein the modified IgG has an increased half-life compared to the half-life of an IgG having the wild-type human IgG constant domain, and wherein the amino acid substitution at amino acid residue 252 is a substitution with tyrosine, the amino acid substitution at amino acid residue 254 is a substitution with threonine, and the amino acid substitution at amino acid residue 256 is a substitution with glutamate. Independent claim 89 recites a modified IgG comprising a human IgG constant domain comprising amino acid substitutions relative to a wild-type human IgG constant domain at amino acid residues 433, 434 and 436, wherein the modified IgG has an increased half-life compared to the half-life of an IgG having the wild-type human IgG constant domain, and wherein the amino acid substitution at amino acid residue 433 is a substitution with lysine, the amino acid substitution at amino acid residue 434 is a substitution with phenyalanine, and the amino acid substitution at amino acid residue 436 is a substitution with histidine.

Independent claim 90 recites a modified IgG comprising a human IgG constant domain comprising amino acid substitutions relative to a wild-type human IgG constant domain at amino acid residues 252, 254, 256, 433, 434 and 436, wherein the modified IgG has an increased half-life compared to the half-life of an IgG having the wild-type human IgG constant domain, and wherein the amino acid substitution at amino acid residue 252 is a substitution with tyrosine, the amino acid substitution at amino acid residue 254 is a substitution with threonine, the amino acid substitution at amino acid residue 256 is glutamate, the amino acid substitution at amino acid residue 433 is a substitution with lysine, the amino acid substitution at amino acid residue 434 is a substitution with phenyalanine, and

the amino acid substitution at amino acid residue 436 is a substitution with histidine. Independent claim 91 recites a modified IgG comprising a non-human IgG constant domain comprising one or more amino acid substitutions relative to a wild-type non-human IgG constant domain at one or more amino acid residues 251-256, 285-290, 308-314, 385-389 and 428-436, wherein the modified IgG has an increased half-life compared to the half-life of an IgG having the wild-type non-human IgG constant domain, and wherein an amino acid substitution at amino acid residue 252 is a substitution with tyrosine, phenylalanine, tryptophan or threonine, an amino acid substitution at amino acid residue 254 is a substitution with threonine, an amino acid substitution at amino acid residue 256 is a substitution with serine, arginine, glutamine, glutamate, asparate, alanine, asparagine or threonine, an amino acid substitution at amino acid residue 309 is a substitution with proline, an amino acid substitution at amino acid residue 311 is a substitution with serine, an amino acid substitution at amino acid residue 433 is a substitution with lysine, arginine, serine, isoleucine, proline, glutamine or histidine, and an amino acid substitution at amino acid residue 434 is a substitution with histidine, asparagine, arginine, threonine, lysine or methionine.

Contrary to the Examiner's contention, Ward does not teach amino acid substitution with threonine at amino acid residues 252, 254 and 256 of an IgG constant domain. Rather, Ward teaches substitution of another residue, in particular, leucine, for threonine at amino acid residue 252, substitution of another residue, in particular, serine, for threonine at amino acid residue 254, and substitution of another residue, in particular, phenylalanine, for threonine at amino acid residue 256 of an IgG constant domain. None of the pending claims recite the substitution of leucine for threonine at amino acid residue 252, the substitution of serine for threonine at amino acid residue 254, and the substitution of phenylalanine for threonine at amino acid residue 256 of an IgG constant domain. Rather, the pending claims 87 and 91 (and claims dependent therefrom) specify particular amino acid substitutions at amino acid residues 252, 254, 256, 309, 311, 433 and 434 of a human or a non-human IgG constant domain which are not described by Ward. Pending claim 88 (and claims dependent therefrom) specifies particular amino acid substitutions at amino acids 252, 254 and 256 of a human IgG constant domain which are not described by Ward. Pending claim 89 (and claims dependent therefrom) describes particular amino acid substitutions at amino acid residues 433, 434 and 436 of a human IgG constant domain which are not described by Ward. Further, pending claim 90 (and claims dependent therefrom) specifies particular amino acid substitutions at amino acid residues 252, 254, 256, 433, 434 and 436 of a human IgG constant

domain which are not described by Ward. Thus, the pending claims are not anticipated by Ward.

In view of the foregoing, Applicants assert that the rejection under 35 U.S.C. § 102(e) has been overcome and, therefore, respectfully request that the rejection be withdrawn.

5. THE REJECTION UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 3, 15, 19 and 86 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ward in view of Taylor et al., U.S. Patent No. 6,572,856 ("Taylor"). The Examiner contends that it would have been obvious to a person of ordinary skill in the art at the invention was made to apply the teaching of SYNAGIS® in Taylor to the teaching in Ward regarding a modified IgG to obtain a claimed modified IgG which has the heavy chain variable domain and light chain variable domain of SYNAGIS®. For the reasons detailed below, the rejections under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

A finding of obviousness requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere 383 U.S. 1 (1996). The proper inquiry is whether the art suggests the invention, and whether the art provides one of ordinary skill in the art with a reasonable expectation of success. In re O 'Farrell 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. In re Vaeck 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed above, in order to expedite prosecution of the present application and without conceding to the validity of the rejection, Applicants have canceled claims 3, 15, 19 and 86,without prejudice, and have added new claims 87-90, 93, 104 and 105. New independent claims 87-90 are directed to a modified IgG comprising human IgG constant domain comprising amino acid residue substitutions at specific positions. Dependent claim 93 specifies additional particular amino acid substitutions. Dependent claim 104 specifies that the modified IgG immunospecifically binds to an RSV antigen. Dependent claim 105 specifies that the antibody has the heavy chain variable domain and light chain variable domain of palivizumab (*i.e.*, SYNAGIS®).

Neither Ward nor Taylor teach or suggest a modified IgG comprising a human IgG constant domain comprising the substitutions recited in independent claims 87-90 (and claims dependent therefrom). The focus of Taylor is the production and use of anti-C3b(i) antibodies for the prevention and treatment of a variety of disorders. As part of the teaching of the use of anti-C3b(i) antibodies, Taylor teaches combination therapy comprising anti-C3b(i) antibodies and SYNAGIS® to prevent or treat a viral infection. Taylor does not teach or suggest introducing substitutions into the constant domain of SYNAGIS® to produce a modified SYNAGIS® with increased half-life. Moreover, there is no suggestion in Ward to introduce the amino acid substitutions recited in the pending claims into SYNAGIS®. Thus, Applicants respectfully assert that Ward in view of Taylor does not render the claimed invention obvious. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants believe that the present claims meet all the requirements for patentability. Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Withdrawal of all rejections and consideration of the amended claims are requested. An allowance is earnestly sought.

If any issues remain, the Examiner is requested to telephone the undersigned.

Respectfully submitted,

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